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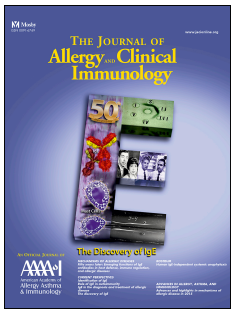

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Letter to the Editor

Mast Cell Activation Syndrome: Importance of Consensus Criteria and Call for Research

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To The Editor:

Mast cell activation syndrome (MCAS) as defined by existing consensus criteria is a condition characterized by mediator-related symptoms associated with a substantial systemic activation of mast cells (MCs) (1,2). Referrals to centers with experience in MC disorders of individuals with the diagnosis of MCAS have recently dramatically increased. The patients referred often do not meet the definition of MCAS and have often undergone extensive evaluations. Referral centers frequently find that in the face of these extensive prior evaluations and in the absence of evidence that MCs are involved, they have little to offer. This letter is written to summarize this situation and propose a way forward.

Originally, and to develop a uniform and thoughtful basis for the clinical study and diagnosis of MCAS, a consensus group consisting of an international panel of allergy, hematology, pathology and dermatology specialists met and introduced diagnostic criteria for MCAS based on the logic that if MCs are responsible, then clinical data must support the involvement of the MC compartment (1,2). The consensus group set forth criteria for the diagnosis of MCAS to include the following: First, the episodic occurrence of typical MC-related clinical symptoms, such as urticaria, angioedema, flushing, pruritus, nausea, hoarseness, vomiting, diarrhea, abdominal cramping, hypotensive syncope, tachycardia, wheezing, conjunctival injection, nasal congestion, and headache. To meet this first diagnostic criterion, the episodic occurrence of such symptoms affecting two or more organ systems should be observed (1,2). Second, an increase of the serum tryptase level by 20%

over the individual baseline plus 2 ng/ml total (e.g. from 10 ng/ml to at least 14 ng/ml; or from 30 ng/ml to at least 38 ng/ml) within a 4-hour window after the reaction. Third, a clear response (improvement) of the symptoms to drugs targeting MC derived mediators and/or MC stabilizing agents (2). When these criteria are met in patients with systemic mastocytosis, by consensus, MCAS is referred to as primary or clonal MCAS. MCAS is also observed in patients with evidence of clonal MC not fulfilling criteria of mastocytosis (3,4). When fulfilled in patients with IgE-dependent allergic reactions or other reactive processes, the term applied is secondary MCAS (Table 1) (1,2). When no underlying etiology is identified, the diagnosis is idiopathic MCAS (2). MCAS criteria are widely accepted and have been validated in specific situations (5).

The diagnosis of MCAS is currently being applied to patients with unresolved complex medical problems following extensive medical evaluations, and a substantial number of these patients do not meet the diagnostic criteria for MCAS. Once the referral center providers eliminate diseases in the differential diagnosis, they find they have little to add in the way of providing a satisfactory response or therapy as no MCAS is found. In other cases, an underlying disease unrelated to MCAS is (later) detected, and an unnecessary delay of such a diagnosis may be a consequence of the ´MCAS-referral´.

Finally, the suggestion to patients that they have a MC disorder beyond (or in addition to) MCAS is not without consequences. Suggestion of a MC disorder may lead to unjustified anxiety and fear for patients, especially when the concept of MCAS is understood as synonymous to systemic mastocytosis, which can lead to hematological malignancy. Moreover, in those without typical clinical symptoms, there may be increased costs and health care utilization in an effort to implicate MCs in pathology.

Is it possible that there are MC diseases outside of what we currently understand? Certainly this possibility exists. There are individuals with chronic symptoms who do not appear to flare in the classical sense. One example is hereditary (familial) tryptasemia, where tryptase is consistently elevated and where many patients complain of non-episodic itch, hives and abdominal pain (6). This more recent discovery raises the possibility that there

may be people for whom other mediators are elevated chronically and other cell types additionally involved, either locally of systemically. Another such example is elevated tryptase in patients with a myeloid or eosinophil neoplasm who may have clonal MCs and similar symptoms, including pruritus, abdominal pain and skin rashes.

The solution to this emerging problem, we suggest, is four-fold. First, caution is needed in applying the diagnosis of MCAS; and consensus criteria should be met (1,2). MCAS should not be applied on the basis of a persistently elevated basal serum tryptase level and not on the fact that the condition has resisted previous attempts to establish a medical diagnosis.

Secondly, if the diagnosis is applied, referral centers must be prepared to evaluate these individuals and eliminate diseases in the differential diagnosis. It is important to recognize that other pathologic conditions, including sepsis, cytokine storm associated with administration of biologics, acute intoxication, poisoning, and endocrinology emergencies may mimic MCAS (2). And in those with elevated basal tryptase, diverse hematologic neoplasms, chronic inflammation or familial tryptasemia may be detected (2). Third, referral centers must implement a follow-up plan for monitoring and care of these patients and/or until a research protocol is in place to understand the difficulties that lead to this diagnosis. Fourth, clinical research programs are needed to explore the possibility that there are yet to be defined MC activation disorders. Such studies need to evaluate the consensus criteria for MCAS. Strategies need to be in place to identify specific phenotypes/endotypes with underlying genetic variants that will lead to uniform diagnostic approaches. Interventional trials with agents known to decrease MC numbers or MC mediator release and the downstream actions of these mediators are needed. Subjects for discussion include consideration of the possibility that there are chronic and local forms of MC activation not fulfilling MCAS criteria where patients present with multiple symptoms and how to document such a possibility? Are there unrecognized MC diseases that involve tissue specific or regional MC activation? Are there additional clinically useful markers of MC activation and how can these conditions be defined?

Currently only a few biomarkers are recognized as implicating MC activation in pathology. One example is histamine or its metabolites when measured in urine, although histamine is produced by MC and basophils. Measurement of tryptase in bodily fluids is more specific and is generally considered the most reliable diagnostic test of MC involvement and thus strongly recommended within consensus diagnostic criteria (1-2,7). Prostaglandin D2 and histamine metabolite levels in urine can both increase over baseline in MCAS and have also been measured and used as guide for treatment (8), although their elevation may not always be associated with MC activation (2). Chromogranin A is not produced by MC in mastocytosis and thus is not a reasonable marker of MC activation. Similarly, plasma levels of heparin have not been generally demonstrated to be a sensitive or specific biomarker for MC activation, although this requires further study.

With the goal of alleviating patients suffering, a balanced approach is thus clearly warranted to both deal with current issues surrounding patients with suspected MC disorders and to promote well-designed and thoughtful prospective clinical research protocols to answer these critical questions (9).

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Table 1

Estimated percent of patients with a specific disorder (underlying condition) that have events that meet the diagnostic criteria of MCAS*

Disorder/underlying condition	Estimated % of those that have events meeting the definition of MCAS
Cutaneous mastocytosis (CM)	10
Systemic mastocytosis (SM)	10-20
KIT D816V+ mast cells without CM or SM	unknown
CM or SM with concomitant allergy	30-50
IgE-dependent allergy	10-20
IgE-independent allergy	unknown
Acute drug hypersensitivity reactions	10-20
Intoxications**	1-3
Acute infections	1-3
Acute autoimmune disease episode	1-3
Sickle cell disease – acute episode	1-3
Solid tumors	<1
Clonal myeloid neoplasms/leukemia	<1
Clonal lymphatic neoplasms/leukemia	<1
Neurologic disorders***	<1
Hereditary metabolic disorders	<1
Diabetes mellitus	<1
Ehlers-Danlos syndrome	<1

*MCAS based on MCAS-criteria as defined in Valent et al. (2). The frequency of MCAS was estimated on the basis of published results and data presented in conferences in the years 2010-2018. Experience may differ substantially depending on the referral center. **Food intoxication resulting from high histamine content (e.g. scombroid fish poisoning) can mimic MCAS, unless pre- and post-event tryptase levels were measured. ****Including autonomic dysfunction such as postural tachycardia syndrome and gastrointestinal motility disorders.